The Natural History of Mycosis Fungoides

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• Mycosis fungoides is a progressive, fatal disease. Its relationship to lymphoblastomas is definite.

No specific treatment is available. Palliation may be brought about by many unrelated modalities.

MYCOSIS FUNGOIDES was first described as an entity by the French dermatologist, Alibert, in 1806.[22] Between that date to 1936, 546 cases were reported in the world literature.[15] Alibert named the disorder *pian fungoide* because of the resemblance to yaws, but at a later date (1835) he used the appellation *mycosis fungoides*. The term *mycosis* was used to describe the mushroom-like tumors; there was no intention of suggesting that a fungus might be an etiologic factor. In 1885, Auspitz introduced the term *granuloma fungoides* because of his belief that the disease represented an inflammatory reaction of the reticuloendothelial system.

Also in 1885, Vidal and Brocq first described the d'emblee form, in which tumors are the initial lesions. Besnier and Hallopeau, in 1892, described the premycotic erythematous stage.

THE NATURAL COURSE OF MYCOSIS FUNGOIDES

Clinically, mycosis fungoides occurs in three stages, the erythematous, the plaque and tumor stage.

The erythematous stage, also known as the premycotic phase, is one of widespread or localized areas of erythema or dry "eczema." The eruption may simulate eczema, psoriasis or parapsoriasis for some time. Poikiloderma-like changes of the skin may occur in the erythematous stage. The erythematous stage may last for months to several years before progressing into the plaque stage. This is characterized by sharply demarcated, slightly elevated lesions, oval or circular in shape and may persist for months to years before progressing into the tumor stage (terminal phase). The tumors usually appear at the sites of the plaques; they may grow slowly or rapidly and many of them eventually ulcerate. Occasionally, tumors may develop without the previous presence of erythematous or plaque lesions (d'emblee type). All stages of the disease may be seen at one time in the same patient. Bullous lesions are rarely present; the bullae arise from normal skin rather than from preexisting plaques.[7]

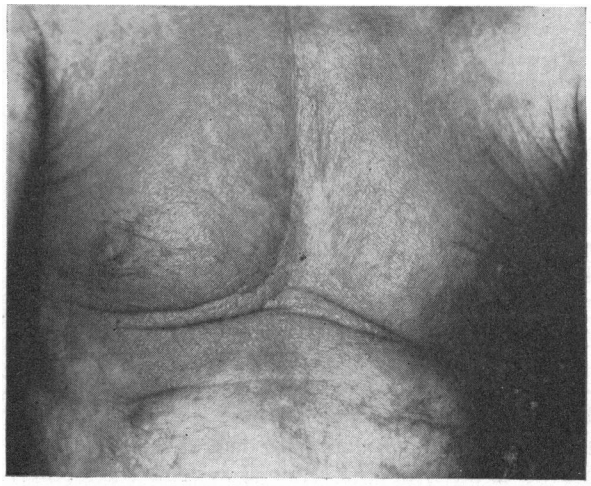

Figure 1.—Erythematous stage of mycosis fungoides. Note erythema and thickening.

Mycosis fungoides is not a transition from psoriasis or parapsoriasis. Although some reports associate psoriasis with the premycotic stage, there are only three proved cases of psoriasis occurring concurrently with myocosis fungoides.[19] In cases in which parapsoriasis is reported to have terminated in mycosis fungoides, the patients actually had a premycotic stage of mycosis fungoides which was dormant for many years before evolving into the plaque and tumor stage. It is unlikely that two different diseases are present in the same patient.[18]

The familial incidence of mycosis fungoides has been noted but is extremely rare.[3] Cawley reported an equal incidence among male and female patients.[3] The disorder occurs less frequently in the Negro than in the Caucasian race.[13,23] The average duration of life after the diagnosis is confirmed is three to six years. Some patients survived for as long as 35 years.

Pruritus is a prominent clinical symptom. It appears early in the erythematous stage and is usually

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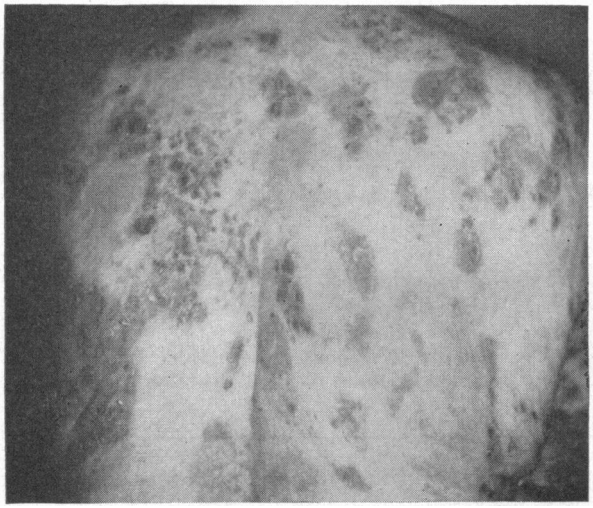

Figure 2.—Plaque stage of mycosis fungoides. Note circumscribed plaques. Similar lesions are present on the chest and extremities.

intense. Rarely the pruritus may appear before the eruption.

The cause of death is intercurrent infection, cachexia or lymphoblastomatous involvement of vital internal organs.

HISTOGENESIS AND PATHOLOGY

Mycosis fungoides is usually placed within the lymphoblastoma group of disorders. This group embraces malignant growths that arise in multiple foci from the lymphoid-reticular system. The mother cell of the lymphoid-reticular system is the lymphoid reticular stem cell found in the lymph nodes, spleen and liver; this may differentiate into either a lymphocyte or a reticulum cell.[17] While the variety of cell types found in the dermal infiltrate includes histiocytes, reticulum cells, lymphocytes, neutrophils, eosinophils, plasma cells and fibroblasts, it is the reticulum cells that may show atypical features. It is likely that in lymphomas of the skin the immature cells arise within the skin, whereas, in nonmalignant dermatoses, cellular infiltrations are hematogenous in origin.

In the early (erythematous) stage the histopathologic features are usually nonspecific, the changes resembling those of chronic dermatitis. After a variable period, there appears an infiltrate limited to the upper portions of the dermis. It is extremely dense and extends to the dermal-epidermal junction. There is a multiplicity of cell types within this infiltrate—histiocytes, reticulum cells, fibroblasts, neutrophils, eosinophils, lymphocytes and plasma cells. The reticulum and histiocytic cells may be atypical in appearance; there may be pyknosis, karyorrhexis, clumping of nuclei (mycosis cells) and mitotic figures. "Abscesses," composed of lymphocytes and

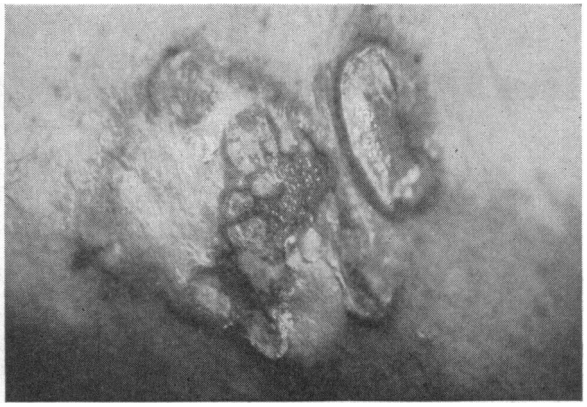

Figure 3.—Tumor stage of mycosis fungoides.

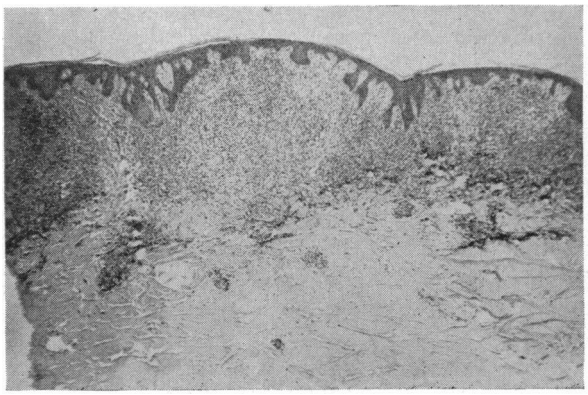

Figure 4.—Section of cutaneous lesion of mycosis fungoides (×30). Note pronounced infiltrate extending throughout entire length of section and involving the upper half of the dermis.

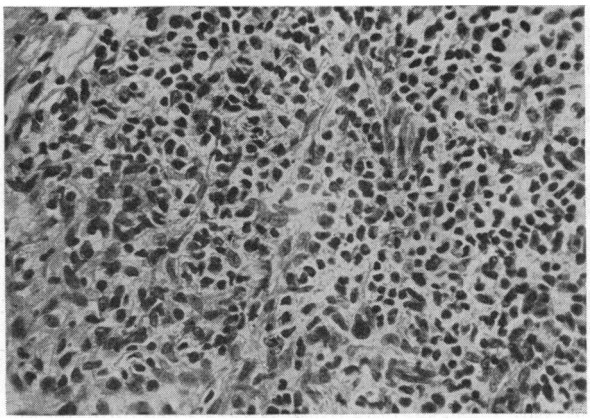

Figure 5.—Section of cutaneous lesion of mycosis fungoides (×400). Infiltrate shows a high percentage of reticuloendothelial cells of varying sizes and shapes.

histiocytes, occur in the epidermis; this is a corroborative, but not a constant finding. The epidermis shows no diagnostic changes, but constant findings are acanthosis, elongation of the rete ridges and an indistinct dermal-epidermal junction. The giant cells of mycosis fungoides referred to as mycosis cells are brought about by clumping of reticulum cell nuclei

or endothelial cell nuclei. They must be differentiated from Reed-Sternberg cells, which are mononucleated or multinucleated giant cells with a dark, nuclear ring, a thick, coarse, nuclear pattern, and a large deep-staining nucleolus. In contrast, the nuclei of mycosis fungoides cells are pale, have a fine chromatin pattern and tiny nucleoli. Spontaneous resolution of plaques and tumors occurs when the infiltrate is absorbed; and, if there is no ulceration, resolution may occur without fibrosis. The infiltrate is invasive rather than destructive.

In necropsy reports of cases in which there was visceral involvement, it was noted that histopathologic features were compatible with lymphosarcoma, reticulum cell sarcoma or Hodgkin's disease.

ETIOLOGY

There is no agreement regarding the cause of mycosis fungoides. Neoplastic, infectious and inflammatory concepts have been proposed.

With regard to the concept of neoplastic origin, the histological features are impressive, for they are similar to those of reticulum cell sarcoma, lymphosarcoma or Hodgkin's disease. The involvement of the internal organs and the response to chemotherapeutic agents used in the treatment of lymphomas suggests a neoplastic disorder.[5,6,21,28]

Investigators who believe an infectious process is an etiologic feature point to animal experiments in which inoculation with freshly excised tumors results in development of lesions that are histologically similar to the original pathologic tissue.[24,25]

To support an inflammatory histogenesis it has been pointed out that there is no destruction of tissue, and also that it is difficult to conceive of a neoplasm with so many diverse cell types.[5,6,28]

Involvement of Internal Organs

Mycosis fungoides is primarily a cutaneous disease. However, in the later stages, involvement of the internal organs may occur. The organs involved most frequently are the lymph nodes, spleen and liver. In approximately 20 per cent of cases of mycosis fungoides in which autopsy is done involvement of viscera is observed.[17] Because of the multicentric origin of mycosis fungoides in the skin, it is conceivable that it arises *de novo* in the internal organs rather than as a metastatic phenomenon. There has been one case reported of internal involvement without skin manifestations.[4]

The Bone Marrow and Blood in Mycosis Fungoides

The bone marrow is not involved in mycosis fungoides.[26] Lapiere and deWeirdt studied the bone marrow in eleven cases of mycosis fungoides and found reticuloendothelial reaction consisting of an increase in the proportion of monoblasts, lymphocytes and plasma cells. They concluded that this reaction was not specific for mycosis fungoides. Santoianni reported similar observations in four cases. Tilley and Smith noted no significant bone marrow changes in six cases they studied.[26]

Autopsy reports on cases in which transformation to a malignant lymphoma has occurred have noted involvement of the bone marrow with neoplastic cells.[3] Eosinophilia is observed occasionally in peripheral blood, but it is not diagnostic.

Roentgenology

There are no definite roentgenographic features that might help diagnostically in the absence of skin lesions. Occasionally, pulmonary infiltrations or enlarged hilar nodes are detectable in known cases of mycosis fungoides.[2,3,20]

Mucous Membrane Lesions

Mucous membrane involvement is extremely rare. In the case reported by Cawley[3] many lymphoblasts were noted in microscopic examination of tissue from lesions of the oral mucosa.

THERAPY

Until 1903, therapy was symptomatic and of little benefit. Then x-ray was used for the first time in the treatment of mycosis fungoides, and to date it has proved to be the most efficacious mode of treatment, resulting not only in palliation but in regression of plaques and tumors. Other forms of therapy that bring about palliation or regression of lesions include administration of tartar emetic, para-aminobenzoic acid, nitrogen mustard, adrenocorticotropin hormones, steroids and varieties of beta and gamma ray radiation, such as radium, radioactive phosphorus and high energy electrons.

The main exponent of tartar emetic therapy is Garb,[8,9,10] who advised two to three injections weekly of 5 cc. of 1 per cent solution intravenously for six weeks. The main advocate of para-aminobenzoic acid is Zarafonetis,[29] who recommended the use of 18 to 24 gm. daily for an indefinite period.

Nitrogen mustard may be given intravenously or orally. The intravenous dose is 0.4 mg. per kilogram of body weight. The oral dose is 0.1 mg. per kilogram. The average duration of relief is three to five months.[10,11,14,16,29]

Treatment with high energy electrons has been used within the past several years.[12,27] The high energy apparatus uses force varying from two to three million volts. At two million volts maximum ionization occurs at a depth of 4 mm. and the ionizing energy is completely dissipated at a depth of 10 mm. In this form of therapy, the ionization at

the surface is half that at the 4 mm. depth, resulting in a remarkable sparing of the surface epidermis.

DATA ON TWENTY-SIX CASES

Following is data on clinical features, laboratory studies and treatment, gathered in observation of 26 cases of mycosis fungoides.

Age at Onset. The average age at onset was 54 years. The youngest patient was 35 and the oldest 74. Mycosis fungoides appeared most frequently in the fourth and fifth decades of life.

Site of Initial Eruption. The disorder usually appeared on the trunk and extremities. Less frequently, only the trunk or only the extremities were involved. In 14 cases there was generalized eruption at the outset. In eight there was involvement of the extremities only and in four involvement of the trunk only.

Type of Initial Lesions. Twenty of the patients had plaques or patches (erythematous or eczematoid) as the initial lesions. Three had nodules only. Two patients had ulcerated tumors (d'emblee form) as the first symptom. One patient had all types of primary lesions when first examined. One had bullae as well as plaques as the first lesions.

General Physical Observations. Only occasionally and coincidentally were abnormal physical findings (exclusive of the skin) noted upon first examination. Two patients had essential hypertension. Two others were febrile and acutely ill and had generalized enlargement of lymph nodes. One of the acutely ill patients improved promptly following therapy with para-aminobenzoic acid. With the exception of the two cases mentioned, acute illness and incapacitation were seen only in terminal stages of the disease.

Blood Studies. Twenty-one patients had total leukocyte content ranging from 5,000 to 10,000 per cu. mm. of blood and four had more than 10,000. One patient had leukocyte content as high as 100,000 per cu. mm.; these cells were interpreted as reticuloendothelial cells, and in a bone marrow study no abnormality was noted.

Nine patients had banded forms of neutrophils in proportions varying from 5 to 40 per cent of total leukocytes. This occurred in patients with normal leukocyte content, and it is difficult to ascribe this to infection alone, for it occurred consistently in the absence of any visible active infection. Only five patients had eosinophil content above 5 per cent.

The blood cell differential in mycosis fungoides in our series showed an increased number of banded neutrophils and, less regularly, an increased proportion of eosinophils, but was otherwise within normal limits.

Bone Marrow. In nine cases data on examination of bone marrow was available. In seven cases the findings were normal and in two there was hypoplastic marrow due to chemotherapy or x-ray therapy.

X-ray Examination of Chest. X-ray films of the chest were available for study in 17 cases. In 13 cases no abnormalities were seen. In two there was peritracheal and hilar adenopathy, and in two others there were scattered densities in both lung fields. In one patient with pulmonary densities, the densities resolved two weeks after nitrogen mustard was given. The other was given nitrogen mustard ten days before death, and at autopsy pulmonary abscesses were observed but there was no evidence of an infiltrate characteristic of mycosis fungoides or lymphoma.

Duration. The average duration of mycosis fungoides from the time of onset (as determined from the history in each case) to the time of death was 6.7 years. The average duration from the time of diagnosis to the time of death was 3.7 years.

Therapy. All patients in the series received superficial x-ray therapy at some time during the course of the disease. It was invariably effective initially, but with each course the results were less effective.

Nitrogen mustard in eight patients was effective for periods of from one to several months. It was administered both intravenously and orally. The intravenous dose was 0.4 mg. per kilogram of body weight injected into the tubing of an intravenous saline drip. In cases in which improvement occurred, it was noticed within seven days: Pruritus regressed and the tumors and plaques began to involute. Occasionally, a second injection was given six weeks later. The oral dose of nitrogen mustard, 0.1 mg. per kilogram of body weight per day, was given for two months, then was discontinued two months and was resumed until evidence of failure or improvement in the clinical status was apparent. Total dosage in any one case varied between 800 and 1,000 mg. The leukocyte content was watched closely and the drug was discontinued when the number of cells dropped below 3,000 per cu. mm.

Para-aminobenzoic acid was administered to four patients. In two patients the plaques and tumors regressed. The dose used was 18 gm. daily. To minimize side effects due to salt retention, the potassium salt of para-aminobenzoic acid rather than the sodium salt was used.

Antimony potassium tartrate was given intravenously to five patients with no success. One patient was treated with the high-energy electron beam (by Dr. John Fromer at the Lahey Clinic) with remarkable regression of plaques and tumors. After four months, several plaques reappeared. The patient was still under observation at the time of this report.

Adrenocorticotropin hormones and steroids (pred-

nisone and prednisolone) were used in 40 to 80 mg. daily doses in two patients. Some regression of the lesions occurred, but the improvement lasted only two to four weeks.

That so many kinds of therapy are used attests that none is consistently effective. Superficial x-ray is the most valuable of them, but the effects are only temporary and palliative. Treatment with high energy electrons is very effective. Since mycosis fungoides is a fatal disease, it is important that each of the modes of therapy mentioned be considered for the individual patient. Each may be effective in a small proportion of patients for periods varying from three to twelve months.

Postmortem Examination. Autopsy was done in seven cases. Only one of the subjects had lesions limited to the skin and six had involvement of the internal organs varying in degree from scattered focal infiltrates to extensive involvement of the viscera. In two there was extensive involvement of the spleen, liver, kidney, colon and heart; in one the lesions were diagnosed as lymphosarcoma and in the other as reticulum cell sarcoma. The cause of death in these two instances was attributed directly to the lymphomatous process.

The remaining four subjects had scattered focal cellular infiltrates in the lymph nodes, spleen and liver. In two subjects with focal infiltrates the lesions were diagnosed as reticulum cell sarcoma and lymphosarcoma respectively. The remaining two showed polymorphous focal infiltrates.

The cause of death in the seven cases in which autopsy was done was as follows: Infiltration of vital organs, aplastic anemia (from x-ray or chemotherapy), acute heart failure, bacteremia and pneumonia. In two instances death could be attributed directly to the lymphomatous infiltration; in the remaining five it could only be indirectly related to the lymphomatous process.

Bone marrow involvement was not present in any of the seven cases in which autopsy was done. In the case of the patient who had leukemic reticuloendotheliosis with normal bone marrow one year before death, there were no bone marrow abnormalities observed microscopically at autopsy.

COMMENT

From analysis of the natural history of mycosis fungoides, it is evident that this disorder may remain relatively dormant from one to twenty years. For reasons unknown, cutaneous tumors may appear at any time. When this occurs, the life expectancy is from six months to two years. Since this is a fatal disorder early treatment is imperative. One should not wait for tumors to appear before treatment is started. Very often, exposure to sunshine or ultra violet light is extremely effective in suppressing the eczematous and plaque-like phase. Other measures which are recommended early in the course of this disorder are administration of para-aminobenzoic acid and tartar emetic. If at all possible, high energy electron therapy should be administered before tumors appear. Active treatment until satisfactory regression occurs seems to offer a better prognosis for life.

The incidence of malignant visceral lymphomatous disease in patients with mycosis fungoides is difficult to determine. Allen[1] in an analysis of necropsy observations in 21 cases reported visceral involvement in three. Cawley[3] reported visceral involvement in eight of ten cases of mycosis fungoides.

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